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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/961,400	09/25/2001	Susanna M. Rybak	018733-1059	6876

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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,400	RYBAK ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-3, 9-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/13/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibit A*.

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Misook Yu.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group 2 encompassing claims 4-8 with species election of SEQ ID NO:2 in the reply filed on 05 April 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-3, and 9-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-18 are pending. Claims 4-8 are examined on merits. Since SEQ ID NO:2 is free of art, the search has been expanded to the other species.

Specification

The use of the trademark ONCONASE® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. Applicant is kindly requested to go over the entire specification very carefully, and to change any occurrence of "Onconase" (note the specification at page 3, Paragraph [0006], for example) to "ONCONASE".

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent

their use in any manner, which might adversely affect their validity as trademarks. Appropriate correction is required.

The specification at page 2, paragraph [003] discloses "Ardelt, et al., J. Biol. Chem. 256:245-251(1991)". However, the volume number of Ardelt, et al., (1991) appears to be incorrect. See below. Since the publication appears to a critical point in the study of ONCONASE® related ribonuclease, a correct citation appears to be very important. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recRapLR1, recRAPLR, or recRACOR linked to a LL2 single chain antibody or to an anti-CD22 antibody, does not reasonably provide enablement for any of the claimed SEQ ID NOs that is not recRapLR1, recRAPLR, or recRACOR. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use and make the invention commensurate in scope with these claims. This enablement rejection has several aspects.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3)

relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the claimed invention is interpreted as drawn to method of killing a malignant B cells with cytotoxic reagent comprising SEQ ID NO: 2, 4, 6, 8, 11, 13, 15, 17, 19, 21, 24, or 26 covalently linked to a ligand binding moiety directed against a cell surface antigen on the malignant B cells (claim 4), to an antibody directed against a cell surface antigen on the malignant B cells (claim 5), to a single chain antibody directed against a cell surface antigen on the malignant B cells (claim 6), to an anti-CD22 antibody (claim 7), to an monoclonal LL2 antibody (claim 8).

The application discloses:

1) The ribonucleases of this invention are isolated from two members of the genus Rana i.e. Rana pipiens liver mRNA library and Rana catesbeiana oocytes. SEQ ID NO:1 represents the nucleic acid sequence of an RNAse derived from a Rana pipiens liver mRNA library. The corresponding amino acid sequence is represented by **SEQ ID NO:2 (RaPLR1)** with **glutamine**.
2) SEQ ID NO:4 is the amino acid sequence of RaPLR1 but with a leucine at position 23 (instead of a methionine).
3) SEQ ID NO:6 is the amino acid sequence of RaPLR1 but with a methionine at the 1 position.

4) SEQ ID NO:8 represents the sequence shown in SEQ ID NO:4 but with a methionine at the 1 position.

5) SEQ ID NO: 11 represents RaPLR1 with a serine at the N-terminus.

6) SEQ ID NO: 13 represents RaPLR1 with a serine at the 2 position and a methionine at the 1 position.

7) **SEQ ID NO: 15** is recombinantly produced protein from Rana catesbeiana oocyte RNAse (**RaCOR1**).

8) SEQ ID NO: 17 is the same amino acid sequence as SEQ ID NO: 15 but with a methionine at the 1 position.

9) SEQ ID NO:19 is the amino acid sequence of SEQ ID NO: 15 but with leucines substituted for methionines at positions 22 and 57.

10) SEQ ID NO:21 is the same as SEQ ID NO:19 except for a methionine at the 1 position.

11) SEQ ID NO:24 represents RaCOR1 but with a serine at the N-terminus.

12) SEQ ID NO:26 is the same as SEQ ID NO:24 except a methionine is at the 1 position.

13) Table 1 at page 61, recombinant Rana pipiens RNAase (Q1S) and recombinant Rana catesbeiana RNAse have activity.

14) At page 62, paragraph [0169], the recombinant Rana pipiens RNAases were active, and the four amino differences in RaPLR1 change the active site configuration such that the N-terminal pyroglutamic acid residue might not be needed for correct hydrogen bonding.

15)At page 62, paragraph [0170] RaCOR1 is also active without the N-terminal pyroglutamic acid.

16)Table 2 discloses recRaPLR1, recRAPLR, recRACOR are cytotoxic to several cell tumor cell lines.

In summary, none of SEQ ID NO: 2, 4, 6, 8, 11, 13, 15, 17, 19, 21, 24 or 26 in the instant claim 4 has pyroglutamic acid at its N-terminal end (position 1), and the specification does not disclose whether each of SEQ ID NO: 2, 4, 6, 8, 11, 13, 15, 17, 19, 21, or 24 has ribonuclease activity. There are 12 new proteins in claim 4, but only 2 or 3 new proteins appear to be tested for their activities. It is not clear which SEQ ID NO in claim 4 is recRaPLR1, recRAPLR, or recRACOR shown in Table 2. It is not clear whether any of the claimed SEQ ID NOs has any ribonuclease activity. The specification discloses recRaPLR1, recRAPLR, and recRACOR are cytotoxic in the vitro cancer cell lines, however, the disclosures at Tables 1-2 do not help evaluate whether any of the SEQ ID NOs has cytoxic activity because rec**RapLR1** could be any one of SEQ ID NO: 2, 4, 6, 8, 11, 13, and recRACOR could be any one of 15, 17, 19, 21, 24, or 26. Or rec**RapLR1** is different from any one SEQ ID NO: 2, 4, 6, 8, 11, or 13. It is the Office's position that rec**RapLR1** and rec**RACOR** in Table 2 have cytotoxic activity, however, the untested SEQ ID NO 2, 4, 6, 8, 11, 13, 15, 17, 19, 21, 24 , or 26 might not have cytoxic activity. The disclosure suggests that rec**RapLR1** and rec**RACOR** are newly discovered ribonucleases and the others in Tables 1 and 2 appear to be art-known ribonucleases.

Sine Ardelt, et al., J. Biol. Chem. 266:245-251(1991) teach at the last line of the abstract that ribonuclease activity of ONCONASE® "seems to be essential for its antiproliferative/cytotoxic effects", each of SEQ ID NOs in claim 4 should have ribonuclease activity in order to be cytotoxic. However, the specification does not disclose whether each of the claimed SEQ ID NOs contains ribonuclease activity.

It is well known in the art that even single amino acid change in a ribonuclease protein structure can have significant and unpredictable effects on biological activity. There is still a great deal of unpredictability in ONCONASE® related ribonuclease activity in terms of which amino acid is in position 1 in relationship with a catalytic site. For example, Newton et al., (1998, Biochemistry vol. 37, pages 5173-83) at the abstract teach unpredictability in enzymatic activity of the recombinant protein in terms of what amino acid is in position 1; adding methionine residue at position 1 in order to better express it in E. coli result in "little enzymatic activity or cytotoxic activity"; this is in accordance with the teaching of the instant application at pages 2-3 i.e. the identity of N-terminal residue is a critical factor for ribonuclease activity of the cytotoxic ribonuclease with antitumor properties. Newton et al., (1998, Biochemistry vol. 37, pages 5173-83, note that the article was published around the time the instant application was filed) teach even single amino acid change at the N-terminus of a recombinant cytotoxic ribonuclease markedly influence biochemical and biological properties. Note the title "Single amino acid substitutions at the N-terminus of a recombinant cytotoxic ribonuclease markedly influence biochemical and biological properties". Newton et al (1998, Biochemistry vol. 37, pages 5173-83) at Fig. 2 teach

only certain amino acid at position 1 works i.e. [Met(-1)]E1S and [Met(-1)] E1Y have ribonuclease activity. Note Table 2 also.

Further, the specification is not clear about recombinant ONCONASE® (col. 1, row 4) in Table 1 at page 61 is same as the recombinant ONCONASE® at paragraph [0169] at page 62, where Newton et al (1997, Protein Engineering, vol. 10, pages 463-70) is referred to. If those two are the same, there seems to be discrepancy between the disclosures of the instant specification at Table 1, paragraph [0169] at page 62, and that of Newton et al (1997, Protein Engineering, vol. 10, pages 463-70).

The instant specification at Table 1 appears to say recombinant ONCONASE® means that Q (glutamine) at position 1 is changed to S (serine). The specification at paragraph [0169] of page 62 discloses recombinant ONCONASE® "with methionine at the position 1". However, Newton et al (1997) at Table 1 do not have any construction of such recombinant ribonuclease.

Further, the sequence search of SEQ ID NO:2 reveals that instant SEQ ID NO:2 is a truncated **putative** ribonuclease according to Chen et al (Nucleic Acids Res. 2000 Jun 15; 28(12): 2375-82). Note the attached sequence alignment of instant SEQ ID NO:2 to the protein sequence of Q918V8 from Sptrembl database (Exhibit A). Chen et al (2000, the peer-reviewed journal article published after the filing date of the instant application from some of the instant inventors) appear to teach whether the full-length ribonuclease comprising instant SEQ ID NO:2 has any ribonuclease activity, has not yet determined.

Next, the claims require various "ligand binding moiety" capable of binding a cell surface antigen on malignant B cells. The specification teaches anti-CD22 antibody that binds to CD22 expressed on malignant B cells. However, the specification does not teach how to make any other ligand binding moiety capable of binding a cell surface antigen on malignant B cells. Arndt et al., (2003, Int. J. Cancer, vol. 107, pages 822-829) teach at page 822, left column that "The B cell lineage specific surface antigen CD22 is only present on a subset of normal mature B cells but strongly expressed by the majority of B cells in B-NHL". This indicates that in order to make another binding moiety capable of binding a cell surface antigen on the malignant B cells, one has to screen a large clinical samples to determine what other surface antigen(s) is expressed on malignant B cells as compared to normal control. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how make the alleged discovery, not how to screen it for themselves.

Further, claim 8 recites a monoclonal antibody LL2. It is apparent that the hybridoma secreting the antibody LL2 is required to practice the claimed invention. As required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the hybridoma that produces the antibody LL2 in claim 8. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the hybridoma secreting antibody LL2, and it does not appear to be readily available

material. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. 112.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Further, at least part of the claimed invention requires a cytotoxic reagent expressed by a recombinant DNA. However, it is not clear how to produce recombinant fusion protein of SEQ ID NO:2 or other other SEQ ID NOs in claim 4, covalently linked to LL2 monoclonal antibody that has to be secreted by a hybridoma. Arndt et al., (2003, Int. J. Cancer, vol. 107, pages 822-829) teach under the heading "MATERIAL AND METHODS" that the variable light and heavy chains of the monoclonal antibody LL2 have been published and one can make LL2 scFv fragment recombinantly, but Mab LL2 appears to be produced by a hybridoma, not by recombinant means.

Considering a great deal of unpredictability in ONCONASE-related ribonuclease enzymatic activity in terms of the N-terminus amino acid identity, the limited guidance as to how to make "a ligand binding moiety" capable of directing the fusion protein to a cell surface antigen on the malignant B cells other than the CD-22 antibody, broad breath of the claims, it is concluded that undue experimentation is required to practice the full scope of the claims.

Claims 4-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This written description rejection is made due to "a ligand binding moiety" being directed against a cell surface antigen on a malignant B cell in claim 4, and claims 5-6 also lack written description for reasons set forth below.

Claims 4-6 are interpreted as drawn to method of killing a malignant B cells with cytotoxic reagent comprising SEQ ID NO: 2, 4, 6, 8, 11, 13, 15, 17, 19, 21, 24, or 26 covalently linked to a ligand binding moiety directed against a cell surface antigen on the malignant B cells (claim 4), to an antibody directed against a cell surface antigen on the malignant B cells (claim 5), or to a single chain antibody directed against a cell surface antigen on the malignant B cells (claim 6).

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The specification defines at paragraph [0050] of page 19 that a ligand binding moiety refers generally to all molecules capable of specifically delivering a molecule, reacting with or otherwise recognizing or binding to a receptor on a target cell.

The specification teaches that an anti-CD20 antibody is a ligand-binding moiety that binds to CD20 antigen on the malignant B cells. The application does not teach a structure of any other "ligand binding moiety" being directed against a cell surface antigen on a malignant B cell.

Arndt et al., (2003, Int. J. Cancer, vol. 107, pages 822-829) teach at page 822, left column that "The B cell lineage specific surface antigen CD22 is only present on a subset of normal mature B cells but strongly expressed by the majority of B cells in B-NHL". This indicates that in order to make another binding moiety capable of binding a cell surface antigen on the malignant B cells, one has to screen a large clinical samples to determine what other surface antigen(s) is expressed on malignant B cells as compared to normal control. Further, Arndt et al., ((2003) under the sub-heading "*Identification of residues modulating stability and homology-modeling*" at page 823 teach that in order to make a single chain antibody directed against a cell surface antigen on the malignant B cells, one has to sequence the variable light chain and heavy chain. The specification does not describe structure of other variable light chain and heavy chain being directed against a different cell surface antigen other than CD22 on a malignant B cell.

There is not even identification of any common structure that has the recited function. Accordingly, in the absence of sufficient recitation of distinguishing identifying

characteristics, the specification does not provide adequate written description of the claimed genus.

A description of a genus may be achieved by means of a recitation of a representative number, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" See page 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116), given that the specification has only described an anti-CD22 antibody. The art appears to possess the single chain antibody from LL2, not any other single chain antibody that has the recited function i.e. "being directed against a cell surface antigen on malignant B cells. Therefore, only anti-CD22 antibody, the single chain antibody from LL2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-

272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642